IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Division of Patent Application Serial No. 09/376,487 of

MISHRA et al — Atty. Ref.: 121-272

Serial No. to be assigned — Group:

Filed: March 23, 2001 — Examiner:

For: INJECTABLE AQUEOUS DISPSERSIONS OF PROPOFOL

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March 26, 2001

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

In order to place the above-identified application in better condition for examination, please amend the application as follows:

IN THE SPECIFICATION

Page 2, after the title insert --This application is a division of U.S. application Serial No. 09/376,487 filed August 18, 1999.--

IN THE CLAIMS

Cancel claims 1 through 12.

15. A method of substantially reducing or eliminating irritation upon injection of a formulation containing propofol comprising administering a stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting

essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent in an aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1, and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and where the dispersion has a viscosity of from about 0.8 to about 15 centipoise.

16. A method of reducing or substantially completely eliminating irritation upon injection of a formulation containing propofol comprising administering a stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, with the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, and the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents.

17. The method of claim 16 where the ratio of propofol to diluent is about 1:4 to about 1:0.1.

18. The method of claim 16 where the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5.

19. The method of claim 16 where the dispersion has a viscosity of from about 0.8 to about 15 centipoise.

20. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthesia- or sedation-inducing amount of a stable, sterile, and antimicrobial injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting

essentially of about 1% to about 15% of propofol, up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, with the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, and the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1, and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the dispersion has a viscosity of from about 0.8 to about 15 centipoise.

21. A method of inducing anesthesia or sedation comprising administering to a subject in need of same an anesthesia- or sedation-inducing amount of a stable, sterile, and antimicrobial injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, and the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents.

22. The method of claim 21 wherein the ratio of propofol to diluent is about 1:4 to about 1:0.1.

23. The method of claim 21 wherein the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5.

24. The method of claim 21 wherein the dispersion has a viscosity of from about 0.8 to about 15 centipoise.

25. The method of any of claims 15, 16, 20, and 21 where the propofol-soluble diluent is one or more selected from isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol, and Miglyol-810.

26. The method of any of claims 15, 16, 20, and 21 where the propofol-soluble diluent is one or more selected from pharmaceutically acceptable natural triglycerides from vegetable or animal sources, pharmaceutically acceptable vegetable oils, and omega-3 polyunsaturated fish oils.

27. The method of any of claims 15, 16, 20, and 21 where the surface stabilizing amphiphilic agent is Lipoid E80, or Lipoid EPC, or Lipoid SPC, or Lipoid SPC-3, or phospholipon-90H or phospholipon-100H.

28. The method of any of claims 15, 16, 20, and 21 where the surface stabilizing amphiphilic agent is 1,2-dimristoyl-sn-glycero-3-phosphocholine, or 1,2-dimristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], or egg lecithin, or egg phosphatidylcholine, or soy phosphatidylcholine, or saturated soy phosphatidylcholine, or soy lecithin, or dimyristoylphosphatidylcholine, or dimyristoylphosphatidylglycerol.

29. The method of any of claims 15, 16, 20, and 21 where the tonicity modifier is sucrose, dextrose, trehalose, mannitol, lactose, or glycerol.

30. The method of any of claims 15, 16, 20, and 21 where the dispersion is suitable for intravenous injection.

REMARKS

Additional claims have been provided which are directed to subject matter disclosed in this application. Basis for these claims is explained in detail in the attachment to this Preliminary Amendment.

An examination on the merits is awaited taking into account the Information Disclosure Statement filed concurrently herewith. Copies of the documents referred to are of record in parent application Serial No. 09/376,487 currently pending in Art Unit 1617.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: ______________________________
Arthur R. Crawford
Reg. No. 25,327

ARC:pfc
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

EXPLANATION OF SOURCE OF NEW CLAIMS

The following claims (claim 15, 16, 17, 18, and 19) are derived from original claim 13 .

15. [The] A **method of reducing or substantially completely eliminating irritation upon injection of formulations containing propofol by administering a stable, sterile, and antimicrobial, aqueous dispersion of water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol** [as the active ingredient], **up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier,** and **the composition being devoid of additional bactericidal or bacteriostatic preservative agents, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1, and the ratio of propofol to amphiphlic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise.**

16. [The] A **method of reducing or substantially completely eliminating irritation upon injection of formulations containing propofol by administering a stable, sterile, and antimicrobial, aqueous dispersion of water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol** [as the active ingredient], **up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity**

modifier, the composition being devoid of additional bactericidal or bacteriostatic preservative agents.

17. The method of claim 16 where **the ratio of propofol to diluent is about 1:4 to about 1:0.1.**

18. The method of claim 16 where **the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5.**

19. The method of claim 16 where **the composition has a viscosity of from about 0.8 to about 15 centipoise.**

The following claims (claim 20, 21, 22, 23, and 24) are derived from the original claim 14 . The term "or sedative effect" in claims 50 and 51 derives from page 7 : "formulations of phospholipid coated microdroplets of propofol devoid of fats and triglycerides that provide anesthesia and chronic sedation ..."

20. [The] A **method of inducing anesthesia** or sedation **comprising administering to a subject in need of same an** [anesthetic]anesthesia- or sedation-**inducing amount of a stable, sterile, and antimicrobial injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol as the active ingredient, up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the composition being devoid of additional bactericidal or bacteriostatic preservative agents, provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise.**

21. [The] A **method of inducing anesthesia** or sedation **comprising administering to a subject in need of same an** [anesthetic]anesthesia- or sedation-**inducing amount of a stable, sterile, and antimicrobial injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of about 1% to about 15% of propofol as the active ingredient, up to about 7% of a propofol soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, and the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the composition being devoid of additional bactericidal or bacteriostatic preservative agents.**

22. The method of claim 21 wherein **the ratio of propofol to diluent is about 1:4 to about 1:0.1.**

23. The method of claim 21 wherein **the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5.**

24. The method of claim 21 wherein **the composition has a viscosity of from about 0.8 to about 15 centipoise.**

The following claims (claim 25 to 30) are derived from dependent claims related to claim 15, above.

25. The method of any of claims 15, 16, 20, and 21 where **the propofol-soluble diluent is one or more selected from isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol, and Miglyol-810.**

26. The method of any of claims 15, 16, 20, and 21 where **the propofol-soluble diluent is one or more selected from pharmaceutically acceptable natural triglycerides from vegetable or animal sources,**

pharmaceutically acceptable vegetable oils, and omega-3 polyunsaturated fish oils.

27. The method of any of claims 15, 16, 20, and 21 where **the surface stabilizing amphiphilic agent is Lipoid E80, or Lipoid EPC, or Lipoid SPC, or Lipoid SPC-3, or phospholipon-90H or phospholipon-100H.**

28. The method of any of claims 15, 16, 20, and 21 where **the surface stabilizing amphiphilic agent is 1,2-dimristoyl-sn-glycero-3-phosphocholine, or 1,2-dimristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], or egg lecithin, or egg phosphatidylcholine, or soy phosphatidylcholine, or saturated soy phosphatidylcholine, or soy lecithin, or dimyristoylphosphatidylcholine, or dimyristoylphosphatidylglycerol.**

29. The method of any of claims 15, 16, 20, and 21 where **the tonicity modifier is sucrose, dextrose, trehalose, mannitol, lactose, or glycerol.**

30. The method of any of claims 15, 16, 20, and 21 where **the dispersion is suitable for intravenous injection.**